

# Drug Therapy of Hypertension

ROBERT F. MARONDE, M.D., and L. JULIAN HAYWOOD, M.D., Los Angeles

IN GENERAL, mortality in hypertension increases in parallel with the blood pressure level.<sup>2,3,9,10</sup> Therefore, any procedure that results in a significant decrease of the hypertension, without concomitant complications that would offset the benefit derived from this decrease in pressure, should lower the death rate. Several investigators have reported that this has been achieved by drug therapy.\* A majority of the patients dealt with in these reports had grade III or IV Keith-Wagner hypertensive retinopathy. In contrast, one hundred patients treated by thoracolumbar sympathectomy and 28 patients treated with drug therapy were studied by the use of matched controls and no decrease in mortality was found.<sup>7,14</sup> In the series dealing with thoracolumbar sympathectomy, data were presented which made it possible to compare the blood pressure levels of the treated and control patients after a ten-year period. Analysis of these data demonstrated that there was no significant difference in average pressure between the two groups. Data by which a similar comparison could be made between the drug-treated group and their controls were not presented.

A definite improvement in the degree of control of the blood pressure as well as a decrease in the side effects from antihypertensive drugs has, in our opinion, occurred within the past two years. It is the purpose of this report to demonstrate the degree of control of the blood pressure of hypertensive patients treated as outpatients.

## METHODS

All patients who attended the hypertension clinic of the Los Angeles County General Hospital in the period of January to April 1960 were selected for this study. In January 1962, patients who were lost from the clinic during this period were traced. In those patients who were still under observation, the average supine and standing blood pressures for the period of January to October 1961 were compared

• Drug therapy can lower the blood pressure levels of most hypertensive patients. The agents now in use are usually better tolerated and more effective than many of those available a few years ago. It seems probable that there is a close relationship between the elevated blood pressure and the increased mortality rate of hypertensive persons and that a significant lowering of this pressure would result in a decrease in mortality.

In a pertinent study, the average pre-treatment blood pressure of a group of 76 patients with moderate to severe hypertension was 198/119 mm. of mercury in the prone position and 192/118 in the standing position. The patients were treated for a two-year period and with treatment their average pressure over a nine-month period was 164/99 mm. prone and 142/94 mm. standing.

Many drugs used for the treatment of high blood pressure have more effect on the lowering of this pressure when the patient is in the standing position. For this reason, the blood pressure, while the patient is standing, should be used as the guide for dosage of these drugs.

---

with control† pressures and with pressures recorded during previous treatment.

Clinic visits were every two weeks, and three observers measured the supine, sitting and standing pressures. Each observer was responsible for an entire visit. Therefore, one observer measured the blood pressure of an individual patient every six weeks. Comparison of the average pressure readings of each observer with the readings of both the others were made and no significant differences for the same group of patients was found.<sup>13</sup> During one period in 1959 and again late in 1961 therapy was stopped in over 40 patients for four to six weeks in preparation for evaluation of new antihypertensive agents. In both instances the average pressure of the patients at the end of these periods did not differ significantly from the control pressures that had been obtained when they first entered the clinic.<sup>11,13</sup> This was true even though a satisfactory response to other antihypertensive agents had been noted for several months. Most of these patients were included in the present study. Under the conditions outlined, we concluded that it was valid to compare the blood pressure levels during the treat-

---

From the Departments of Medicine of the University of Southern California School of Medicine (Maronde), Loma Linda University School of Medicine (Haywood), and the Los Angeles County General Hospital, Los Angeles 33.

Presented as part of a Panel on New Approaches to Diagnosis and Treatment of Hypertension at the 2nd General Meeting at the 91st Annual Session of the California Medical Association, San Francisco, April 15 to 18, 1962.

\*References 1, 4, 6, 8, 15, 16, 17.

†When the patient was first referred to the clinic, control blood pressures were obtained by stopping medication for a period of six to ten weeks, except for patients with active grade III or IV Keith-Wagner hypertensive retinopathy, whose control pressures were obtained from the hospital records.

ment period with the control pressures even though these control levels were obtained at a time that preceded the treatment period.

Our sequence of treatment was: (1) reserpine or a thiazide diuretic; (2) reserpine plus a thiazide drug; (3) a thiazide plus guanethidine, and (4) guanethidine and a thiazide plus reserpine. Supplemental potassium was usually given with the thiazides. The stages in this sequence were separated by approximately six weeks and progression of one schedule to the next was carried out if it was believed that a satisfactory response had not taken place (diastolic pressure of 100 mm. of mercury or below). Guanethidine and a thiazide were given concomitantly because of the more pronounced effect on the supine pressure as compared with the use of guanethidine alone.<sup>12</sup>

### RESULTS

A total of 137 patients were seen in the clinic during the period January to April 1960. Twenty-eight were new patients who were not subsequently treated because they had only mild or labile or systolic hypertension or because they were financially ineligible and were referred to private care. Two additional patients were referred to the hospital at the time of their first visit because of malignant hypertension. Of the remaining 107 patients, 24 were treated but then were lost from the clinic during the period January 1960 to January 1962. All were traced and found to be alive. Twelve were under the care of other physicians or were receiving no therapy. Three of the 24 patients were invalids as the result of cerebral vascular thrombosis or hemorrhage. Another of the group of 24 was in hospital as the result of a traffic accident and still another was in hospital because of renal disease which antedated his first clinic visit. Seven patients of the 24 had been referred to the general medical clinic because of mild or labile hypertension or because of inability to cooperate with or understand the treatment program. There were seven deaths in the 107 patients, three from cerebral vascular disease, two from uremia, one from carcinoma and one from cirrhosis of the liver.

Seventy-six patients were treated and still were under observation in the clinic in January 1962. The average age of this group was 51 years. Sixty-three were Negroes and 60 of the 76 were women. Forty-one had electrocardiographic evidence of left ventricular hypertrophy and 17 were taking digitalis. There were eight with serum urea nitrogen above 25 mg. per 100 cc., and eight patients had grade III or IV Keith-Wagner retinopathy. Eight new patients were accepted for treatment between January and April 1961.

Compilations were made of the average blood pressures of the 68 patients of this group of 76 who were attending the clinic before January 1960. The three-month period preceding January 1960 was selected for this purpose. At that time 30 patients were taking a ganglion-blocking agent plus reserpine and/or a thiazide diuretic. The average pressure for the group was 190/116 mm. of mercury supine and 178/102 standing. Thirty-eight patients received a thiazide and usually reserpine but no blocking agent during the three-month interval. Their average pressures were 172/108 supine and 165/105 standing. It should be noted that many in this group had previously been given ganglion-blocking agents but were unable to tolerate them because of side effects.

In the period January to October 1961, 12 of the 76 patients received only a thiazide diuretic. Their average pressures were 142/92 mm. supine and 136/93 standing as compared with control levels of 180/111 supine and 177/111 standing. Twenty-four patients were treated with a thiazide and reserpine. The average treatment pressures were 157/93 supine and 134/90 standing while the respective control pressures were 194/116 and 188/112. Two patients in this treatment group were unable to tolerate any other antihypertensive agents because of side effects, and their blood pressure control was not adequate. Twenty-one patients were treated with guanethidine and a thiazide. Their average pressures during treatment were 173/102 and 147/94, supine and standing, and their control blood pressures were 204/122 supine and 197/122 standing.

A group of nine more severely ill patients, three of whom had serum urea nitrogen above 30 mg. per 100 cc. and another two with grade III or IV Keith-Wagner retinopathy, were treated with guanethidine and a thiazide plus reserpine. Their control pressures were 208/126 supine and 203/130 standing. The comparable averages during treatment were 184/113 and 160/104. The fact that three antihypertensive agents were used in the treatment of the patients of this group indicates a resistance to therapy (see foregoing description of *methods*). Two of this group of nine patients were unable to tolerate effective doses of guanethidine because of the side effects.

Four patients were treated with reserpine only. Three of them had previously required a blocking agent for a prolonged period to control their blood pressure. It is not frequent, in our experience, that dosages of antihypertensive agents may be greatly reduced once blood pressure control has occurred.

Six patients who were treated with mecamylamine or hydralazine complete the total of 76 patients. The four who received mecamylamine had had adequate control of pressure before January 1960 and their therapy was not changed. The two patients taking

hydralazine could not tolerate guanethidine or ganglion-blocking agents, one because of side effects, the other because of increased elevation of serum urea nitrogen. Neither of these latter patients had a significant change in pressure levels.

#### DISCUSSION

The patients presented here are not a representative sample of the hypertensive population. This is evident by the preponderance of Negroes, the high average blood pressures and the frequency of the electrocardiographic finding of left ventricular hypertrophy. Mortality statistics pertaining to a group of this type are not available but undoubtedly the mortality rate for them would exceed that of the hypertensive population as a whole.

Eight patients of this group had a disappearance of their electrocardiographic abnormalities. No deaths resulted from cardiac decompensation. This is of interest since this has been the cause of approximately 60 per cent of hypertensive deaths.<sup>5</sup> This probable decrease in the incidence of death from hypertensive heart disease is in accord with the report of Sokolow and Perloff.<sup>17</sup> Whether or not drug therapy has influenced the incidence of cerebral vascular lesions or nephrosclerosis is not apparent from the present study. Of the three patients who had non-fatal cerebral vascular episodes all had a poor blood pressure response with antihypertensive agents. However, in two of the three fatal cases of cerebral vascular lesions the blood pressure response to drug therapy had been considered adequate. The 11 patients with serum urea nitrogen levels above 25 mg. per 100 cc. all had evidence of renal disease at the time of their first clinic visit. No real change in these levels occurred in the eight surviving patients during this period of observation. The three patients who died of renal disease came to the clinic with serum urea nitrogen greater than 50 mg. per 100 cc.

Our treatment schedule at present has been slightly modified. Therapy is started with a thiazide and not reserpine. Using the double-blind technique, we were able to demonstrate a slight effect on only the standing diastolic pressure but no effect on the supine pressure or standing systolic pressure when 0.5 mg. of reserpine per day was given over a 12-week period.<sup>13</sup> Other investigators using a similar technique had previously demonstrated that no statistically significant blood pressure change resulted from reserpine by mouth when it was the sole therapeutic agent.<sup>18</sup>

#### CONCLUSIONS

Drug therapy can lower the blood pressure levels of hypertensive patients in the majority of cases. The agents now in use are usually better tolerated and more effective than many of those available a few years ago. It would be difficult to believe that a close relationship between the elevated blood pressure and the increased mortality rate of hypertensives did not exist and that a significant lowering of this pressure would not result in a decrease in this mortality rate.

U.S.C. School of Medicine, 2025 Zonal Ave., Los Angeles 33 (Maronde).

#### REFERENCES

1. A symposium on hypertensive drugs, *Brit. Med. J.*, 1:915, 1956.
2. Bechgaard, Poul: Arterial hypertension, *Acta Med. Scand. Suppl.* 172, 1946.
3. Bolt, W., Bell, M., and Haines, J.: New York Life Insurance Co., Assoc. of Med. Directors of America, 41:61, 1957.
4. Burnett, C. F. Jr., and Evans, J. A.: Drug therapy in hypertension with hemorrhagic hypertensive retinitis, *N.E.J.M.*, 253:395, 1955.
5. Chasis, H., and Golding, W.: Hypertension and hypertensive disease, *The Commonwealth Fund*, 1944.
6. Dustan, H. D., Schneckloth, R. E., Corcoran, A. C., and Page, I. H.: The effectiveness of long term treatment of malignant hypertension, *Circulation*, 18:644, 1958.
7. Evelyn, K. A., Singh, M. M., Chapman, W. R., Perera, G. A., and Thaler H.: Effect of thoracolumbar sympathectomy on the clinical course of primary (essential) hypertension, *Amer. J. Med.*, 28:188, 1960.
8. Freis, E. D., and Wilson, I. M.: Results of prolonged treatment with pentolinium tartrate, *Circulation*, 13:856, 1956.
9. Gubner, R. S.: Hypertension, *Recent Advances*, Lea & Febiger, 1961.
10. Lyle, A. M.: A pilot study of hypertension, *Transactions of the Society of Actuaries*, No. 4, 1954.
11. Maronde, R., Barbour, B., and Haywood, L. J.: Clinical evaluation of guanethidine, *Ann. N. Y. Acad. Sci.* Vol. 88, 990, 1960.
12. Maronde, R. F., Haywood, L. J., and Barbour, B.: Comparison of guanethidine and guanethidine plus a thiazide diuretic, *Am. J. Med. Sci.*, 242:228, No. 2, 1961.
13. Maronde, R. F., Haywood, L. J., Feinstein, D., and Sobel, C.: Evaluation of Pargyline and Pargyline plus reserpine as antihypertensive agents. To be published.
14. Perera, G. A.: Antihypertensive drugs versus symptomatic treatment in primary hypertension, *J.A.M.A.*, 173:11, 1960.
15. Perry, H. M. Jr., and Schroeder, H. A.: The effect of treatment on mortality rates in severe hypertension, *Arch. Int. Med.*, 102:418, 1958.
16. Sears, H. T. H., Snow, P. J. D., and Houston, I. B.: Treatment of hypertension with pentolinium and mecamylamine, *Brit. Med. J.*, 1:462, 1959.
17. Sokolow, M., and Perloff, D.: Five year survival of consecutive patients with malignant hypertension treated with antihypertensive agents, *Am. J. Cardiol.*, 6:858, 1960.
18. Veterans Administration cooperative study on antihypertensive agents, *Arch. Int. Med.*, 106:81, 1960.

YES ON 22